REMARKS

Applicant respectfully requests reconsideration. Claims 28-34 and 36 were previously pending in this application. No claims are amended herein. As a result, claims 28-34 and 36 are still pending for examination with claims 28 and 29 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 103

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al. 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al. U.S. Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al. US. Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994).

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al. 1992 Jpn. Cancer Res. Vol. 83 pgs. 2440247 in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al. U.S. Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al. U.S. Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994).

Kuramoto et al described the use of 30-mer ODN having a particular 6 nucleotide palindromic sequence to induce IFN expression and enhance NK cell activation. A panel of ODN having different sequences and a phosphodiester backbone were tested for activity by incubation with mouse spleen cells. The authors hypothesize that the strong activity of bacterial DNA may be due to the palindromic sequences contained therein.

Kataoka et al. describe the use of palindrome-containing ODN for the treatment and prevention of tumors in mice. ODN were mixed with tumor cells and injected intradermally into mice. According to Kataoka et al. palindrome-containing ODN that were premixed with tumor cells suppressed tumor growth compared to ODN that did not include palindromes. Both the functional and nonfunctional ODN included a CG dinucleotide. Kataoka et al. also describe the production of a local immune reaction at the site of a tumor by injection of palindrome-containing ODN into the

tumor lesion. They note that the antitumor activity of the ODN correlated well with NK and IFN activity.

According to the Examiner, Tokunaga et al. and Goodchild both teach backbone modifications. Applicants disagree regarding the teachings of Tokunaga et al. Tokunaga et al describe the synthesis of ODN "by the standard phosphoramidite method using a 0.2 μmol scale phenoxyacetyl support cassette" (page 56). The protocol described can either deliver a natural backbone or stabilized backbone ODN depending on the type of phosphoramidite monomer used in the coupling reactions and the type of oxidizer used in the oxidation reaction. A standard phenoxyacetyl-protected phosphoramidite monomer in the coupling step followed by oxidation with iodine would result in a non-stabilized natural backbone, while oxidation with a sulfurization reagent would produce a phosphorothioate ODN. Similarly, coupling of a 2'-O-methyl-modified phosphoramidite monomer followed by oxidation with either iodine or a sulfurization reagent would result in a stabilized backbone. However, Tokunaga et al. have only described a standard phenoxyacetyl protected assay, suggesting the production of a phosphodiester backbone ODN. There is no description of the use of a sulferization reagent or a 2'-O-methyl-modified phosphoramidite monomer.

The Examiner has indicated that Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA and that one of skill in the art would have been motivated to modify the ODN of Kataoka et al or Kuramoto et al. to include a backbone modification in order to improve stability or improve uptake Although it was known in the art that phosphorothioate backbone modifications increase stability of an oligonucleotide it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides. At the time of the invention is was not clear how a change in backbone would affect the properties of the immunostimulatory oligonucleotides.

A 1993 *Science* paper by Stein et al (Science v. 261 p. 1004 1993) shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation *in vivo*. As detailed in Stein et

al those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction.

Phosphate backbone modifications were known to have unpredictable effects on nucleic acids. Among the complications introduced by phosphorothioate modification is the creation of stereochemistry. The sulfur in a phosphorothioate modification introduces stereochemistry at each bond where it is present, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. Because stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties. This stereochemistry of phosphorothioates was known prior to 1994. One of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation. This stereochemistry does not occur with the usual oxygen. In addition to the stereochemistry, the sulfur atom can have further effects on the activity of the nucleic acid simply due to its being much larger than the oxygen.

Those of ordinary skill in the art did not know the mechanisms through which the nucleic acids of Kataoka et al. or Kuramoto et al. achieved immune stimulation. Without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids. In the absence of the work of the instant invention it would not have been known at the time of the invention whether a phosphorothioate bond or phosphorodithioate bond would substantially change the shape of the oligonucleotide so as to totally destroy immunostimulatory ability.

In Kataoka et al. or Kuramoto et al., there were palindromes that were inactive, therefore, even though Kataoka et al. or Kuramoto et al. attributed the "activity" of the oligonucleotides to palindromes, it would have been unclear to one of ordinary skill in the art what characteristics of the

molecule were actually critical for activity. In the absence of the teachings of the invention, it would not have been predictable that a phosphate backbone modification to a molecule shown to be "active" in Kataoka et al. or Kuramoto et al would allow the molecule to retain its immune stimulatory effects.

It is further stated in the Office Action that Hutcherson et al teach a composition of an oligonucleotide delivery complex containing a phosphorothioate modified CpG containing oligonucleotide associated with a cationic lipid and that Cheng et al each an oligonucleotide having a phosphorothioate linkage covalently linked to a sterol. It is argued that one of skill in the art would modify the ODN of Kataoka et al or Kuramoto et al by complexing it with a sterol as taught by Chen et al or a delivery complex as taught by Hutcherson et al. Applicants disagree regarding the teachings of Hutcherson et al. Hutcherson et al. does not disclose that the nucleic acids must have a CpG. While the 3 examples of oligonucleotides provided by Hutcherson et al. happen to contain a CpG, those examples do not include the oligonucleotides formulated in a delivery complex. Hutcherson et al. does not teach one of skill in the art that a CpG is required or responsible for immunostimulation. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity.

Even if one of skill in the art would have combined the teachings of the references, Kataoka et al. or Kuramoto et al, Hutcherson et al., Tokunaga et al. Goodchild, and Cheng et al it would not have necessarily produced the claimed invention. Kataoka et al. teach that ODN having a hexameric palindromic motif are effective in reducing tumor size. Some of the functional ODN included a CG in the palindromic motif and others did not. All of the non-functional ODN which did not include palindromic motifs included a CG. One of skill in the art would not have been motivated based on these teachings to use an ODN comprising a 5'CG3' sequence to modulate an immune response. Thus, the claimed invention as a whole was not obvious in view of the combination of the four references.

Double Patenting Rejection

Claims 28 and 36 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122 and

124 of copending Application No. 10/314,578. Specifically Applicants arguments have been dismissed because according to the Examiner MPEP 804 (Chart IIB) depicts a circumstance when common ownership is not present.

Applicants wish to make it clear on the record that the instant application and the cited patent application do not have common ownership, as common ownership is defined in MPEP 706.02(l). MPEP 706.02(l) states that the "term 'common ownership' means wholly owned by the same person(s) or organization(s) at the time the invention was made." Applicants also note that US 10/314,578 is a later filed application, which has now issued as US 7271156. Application of double patenting in a circumstance when the patents are not commonly owned and do not have identical inventorship and the claims under rejection have the earliest effective priority date would be contrary to the public policy reason for double patenting. The public policy behind the double patenting doctrine is to allow the public to freely use a patent upon its expiration. "The basic concept of double patenting is that the same invention cannot be patented more than once, which, if it happened, would result in a second patent which would expire some time after the original patent and extend the protection time wise." *General Foods Corp. v. Studiengesellschaft Kohle MbH*, (972 F.2d 1272, 1279, 23 USPQ2d 1839, 1844 (Fed. Cir.. 1992)). (See also *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) and MPEP 804B). The instant application would not be expected to expire prior to the expiration of the patent applications if they are to issue. Issuance of the instant patent application would not extend the patent protection beyond a point by which the public would otherwise be free to use the technology. Further US 7271156 which has an earliest effective priority date of September 25, 1999 is not prior art under any other section of the statute against the instant applicants or any other party that filed a patent application prior to 1999. To apply a double patenting rejection in the instant circumstance would extend beyond the purpose of the nonstatutory obviousness-type double patenting. Thus, double patenting is not appropriate in the instant circumstance.

Applicants also call to the Exmainer's attention the existence of US 10/769282 which includes overlapping claims. Applicants have previously brought the existence of this patent application to the attention of the examiner and have submitted copies of Office Actions received in that case that were produced by a different examiner.

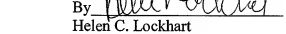
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: June 12, 2008

Respectfully submitted,

By 

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